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THE PATENTS ACT, 1970

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FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

COMPLETE SPECIFICATION
(See section 10)

PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

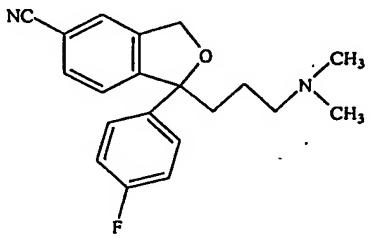
Original
18/MUM/2002
10/11/2002

PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES

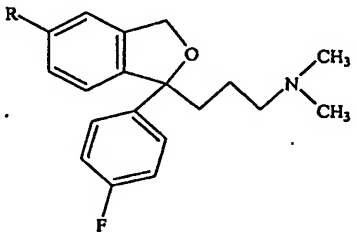
1-[3-(Dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, compound of **Formula I,** commonly known as citalopram (INN Name), is a well known antidepressant. Preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile was first disclosed in United States Patent No. 4,136,193. Subsequently several other patents appeared in the literature regarding enriching crude citalopram base or salt purity so as to obtain pharmaceutically acceptable base or acid addition salts.

PRIOR ART

United States Patent No. 4,136,193 (Indian reference not available, hereinafter referred to as the '193 patent) claims 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable acid addition salt. The '193 patent discloses a process for the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, from the compounds of **Formula II** wherein R is halogen or trifluoromethyl, by reaction with a cyanide source, which is hereinafter referred to as cyanide exchange process.



Formula I



Formula II

The cyanide exchange process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile has been reported (PCT application WO 0145483 and United Kingdom Patent GB 2356199) to give the

desmethylcitalopram and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

United Kingdom Patent No. GB 2356199 (Indian reference not available) discloses preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, by the cyanide exchange process in sufolane solvent, instead of dimethylformamide solvent as in example 2 of the '193 patent. Even using sufolane as a solvent the purity reported by HPLC is about 85%, which is further purified by film distillation process.

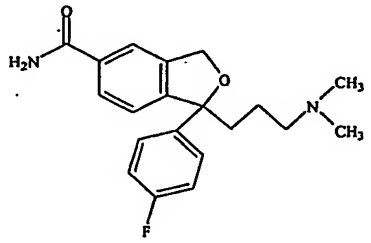
United States Patent US 6455710 (the equivalent is the PCT publication WO 0145483, Indian reference not available) discloses a cyanide exchange process for preparation of pure 1-[3-(dimethylamino)propyl]-1- (4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the compounds of **Formula II,** wherein the group R is selected from chloro, bromo, iodo or $CF_3-(CF_2)_n-SO_2-O-$, n being from 0 to 8, by reaction with a cyanide source and subsequently treating the resultant crude citalopram with an amide or an amide-like group forming agent for removing desmethylcitalopram impurity generated during cyanide exchange process. This United States patent teaches that desmethylcitalopram impurity is removed by reacting with a reagent that converts it into amide or an amide-like neutral derivative, which subsequently can be removed by means of acid base treatment. The reagents like acid halides, acid anhydrides have been disclosed for removal of desmethylcitalopram impurity. Acetic anhydride and acetyl chloride are the preferred reagents and use of only acetic anhydride has been exemplified in US 6455710. These reagents transform basic secondary amine i.e. desmethylcitalopram to the neutral form, wherein the tertiary amine viz., the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile remains unaltered, hence displaying the basic character, thereby making the process suitable to eliminate the desmethylcitalopram that gets transformed into a neutral derivative which can be removed by means of acid base treatment. However, this method does not remove the

carboxamide impurity that is generated during cyanide exchange process hence the disclosure is not a complete solution to improve the efficiency of the process.

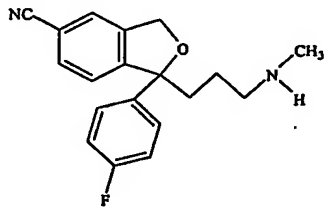
OBJECTIVES OF THE INVENTION

The objective of the present invention is to make 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base in a substantially pure form by removal of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base obtained using cyanide exchange process. When the cyanide exchange process was performed, i.e. the conversion of 5-bromo phthalane derivative to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran, it furnished 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with purity ranging between 75-85% by HPLC (area %). As reported in the patent literature we found it extremely difficult to remove the impurities and to make the desired quality of pharmaceutically acceptable product.

We observed the major impurity that is formed during the course of cyanide exchange process is the amide impurity viz. 5-carboxamide –1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III,** along with desmethylcitalopram impurity viz., 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-(dihydro-5-isobenzofuran carbonitrile, a compound of **Formula IV,** herein after these impurities will be referred to as amide and desmethylcitalopram, respectively.



Formula III



Formula IV

Thus for making 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with acceptable purity, it is essential to have an efficient

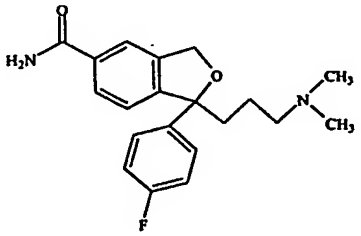
process to avoid the formation of impurities during the cyanide exchange process, or to eliminate the major impurities viz, the amide and the desmethylcitalopram by making suitable derivatives.

The objective of the present invention is conversion of unwanted amide impurity to the desired product viz. to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, along with simultaneous removal of desmethylcitalopram impurity.

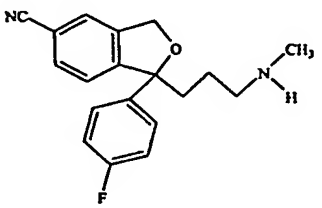
SUMMARY OF THE INVENTION

The present invention provides a process for preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, the process comprising

(a) treating crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base containing the amide impurity viz. 5-carboxamide –1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III,** and the desmethylcitalopram impurity viz., 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3- (dihydro-5-isobenzofuran carbonitrile, a compound of **Formula IV,** with a cyanide reversal agent, wherein the cyanide reversal agent is selected from phosphorous oxyhalides and phosphorous oxides; and



Formula III



Formula IV

(b) isolating 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the reaction mixture,

characterized in that 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile contains less than 1% amide impurity and less than 1% desmethylcitalopram impurity after isolation from the reaction mixture.

The major impurities that are formed when 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile is prepared by cyanide exchange process disclosed in the '193 patent, are compounds of **Formulae III** and **IV**. Presence of these impurities poses difficulty in purifying the crude 1-[3-(dimethylamino)propyl] -1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base to the desired quality of end product.

During the process the amide impurity is formed to an extent of 10%, and normally it ranges from 1 to 10% depending on the reaction conditions. The range of formation of this impurity is wide, hence developing a process which removes the impurity in one unit operation, say crystallisation or distillation or any other purification, proved to be very difficult and unpredictable. Therefore one needs to use multiple solvent crystallisation to obtain the desired product, which makes the whole process lengthy, and also use of several reactors during purification makes it unworthy.

To devise a suitable process in order to improve purity, we envisaged that reaction of reagents, referred to herein as cyanide reversal agents, like oxy compounds of phosporous with the crude base would result in the coversion of the amide impurity to cyanide i.e. the formation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile back from the amide, with concomitant elimination of desmethylcitalopram by forming a neutral species like phosphorous amides.

DETAILED DESCRIPTION OF THE INVENTION:

We found upon treating crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base containing 1-20% of amide and 0.5-10% of desmethylcitalopram with the reagents of phosphorous oxy compounds, like phosphorous oxyhalides and phosphorous oxides, gave substantial enrichment in purity, wherein the amide impurity reduced to below 1% due to reversal of amide to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile and the desmethylcitalopram to below 1%. With phosphorous oxychloride the amide and desmethylcitalopram impurities reduced to below 0.5%.

According to the process of the present invention in step (a) the cyanide reversal agent that is employed is selected from phosphorous compounds such as phosphorous oxyhalides and phosphorous oxides. The halides that can be used are chlorides and bromides, preferred being chlorides. The preferred cyanide reversal agent is being selected from phosphorous compounds wherein phosphorous is with valency [III] or [V], e.g. phosphorous trichloride (PCl_3), phosphorous oxychloride ($POCl_3$), phosphorous pentoxide (P_2O_5). The particularly preferred cyanide reversal agent is selected from phosphorous oxyhalides such as phosphorous oxychloride and phosphorous oxides such as phosphorous pentoxide. The most preferred cyanide reversal agent being phosphorous oxychloride.

The term cyanide reversal agent, as used herein refers to the fact that these agents are capable of

i) reacting with the amide impurity of Formula III and convert it to the citalopram i.e. the amide group in the amide impurity is converted to cyanide group, resulting into formation of citalopram; and

ii) converting the desmethylcitalopram impurity of Formula IV in to a neutral species that can be conveniently removed during work-up,

resulting into citalopram having substantially low levels of impurities.

According to the process of the present invention, in step (a), the ratio of the cyanide reversal agent to the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base is in the range from 0.1 to 5; the preferred range being 0.1 to 2 and the most preferred range being 0.2 to 2.

Preferably, the solvent used in step (a), is an aprotic organic solvent. The aprotic organic solvent may be polar or non-polar. The solvent may be selected from ethers such as tetrahydrofuran, dioxane and the like; halogenated solvents such as dichloroethane, dichloromethane, chlorobenzene, dichlorobenzene and the like; aliphatic hydrocarbons such as hexane, cyclohexane and the like; aromatic hydrocarbons such as toluene, xylenes and the like; esters such as methyl acetate, ethyl acetate, benzyl acetate and the like; nitirles like acetonitrile, benzonitrile and the like; and nitro compounds such as nitromethane and nitrobenzene. The preferred solvents being ethers, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated solvents, esters and nitriles and the most preferred being aliphatic and aromatic hydrocarbons, ester and nitrile solvents. In particular aromatic hydrocarbons such as toluene or xylenes are preferred.

According to the process of the present invention, step (a) can be performed at ambient to 200^{0}C; preferably between 50 to 200^{0}C, and most preferably between 50 to 150^{0}C. The reaction time is, between 1 to 20 hours, preferably between 1 to 15 hours, most preferably between 1 to 5 hours.

The compound 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile may be isolated by adding water to the reaction mixture; then adding an acid until the mixture is acidic, for e.g. until pH is between the range of 1 to 4, preferably between 1 to 3 and most preferably between 2 to 3; and separating the aqueous phase containing 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile; discarding the organic phase containing the neutral species like phosphorous amides that are formed during reaction with the reagents like phosphorous oxychloride; and then making the

aqueous phase basic by addition of a base, and extracting the mixture in an organic solvent and collecting the organic phase to obtain 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile. The acid used may be any mineral acid, for example HCl, HBr or H_2SO_4 or an organic acid, and the base used may be any convenient base such as ammonia or NaOH.

Thus the process developed and described provides a viable method of getting high quality product with better yield, by reversing the amide impurity to the desired 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, and concomitant removal of desmethylcitalopram impurity by forming the neutral species with the cyanide reversal agents. Hence this process obviates use of multiple solvents and operations making it user friendly.

The following examples are given by way of illustration only and not to be construed as limiting

EXAMPLES

Example 1

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 4.7% amide and 0.72% desmethylcitalopram impurities) and phosphorous oxychloride ($POCl_3$) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70^0 C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.05% and 0.23% of amide and desmethylcitalopram respectively.

Example 2

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 5.85% amide and 7.43% desmethylcitalopram impurities) and phosphorous oxychloride ($POCl_3$) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70^0 C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.36% and 0.45% of amide and desmethylcitalopram respectively.

Example 3

A mixture of crude 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 8.27% amide and 0.33% desmethylcitalopram impurities) and phosphorous oxychloride ($POCl_3$) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70^0 C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.07% and 0.12% of amide and desmethylcitalopram respectively.

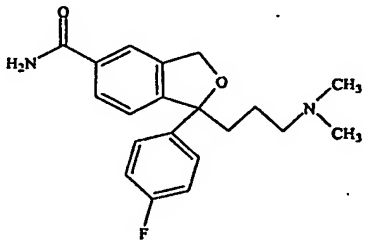
Example 4

A mixture of crude 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(5.0g, 0.01 5mol) (containing 5.8% amide and 1% desmethylcitalopram impurities) and phosphorous pentoxide (P_2O_5) (2.98g, 0.01mol) in xylene (50ml) was stirred at 140^0C under nitrogen atmosphere for 2 hours, poured into water (100ml) and NaOH flakes (5.0g, 0.125mol) was added to make reaction mixture basic, stirred for 30 minutes separated the xylene layer, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.49% and 0.64% of amide and desmethylcitalopram respectively.

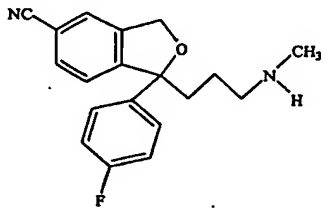
We claim

1. A process for preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, the process comprising

   (a) treating crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base containing the amide impurity viz. 5-carboxamide –1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III,** and the desmethylcitalopram impurity viz., 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3- (dihydro-5-isobenzofuran carbonitrile, a compound of **Formula IV,** with a cyanide reversal agent, wherein the cyanide reversal agent is selected from phosphorous oxyhalides and phosphorous oxides; and



Formula III



Formula IV

   (b) isolating 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the reaction mixture,

   characterized in that 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile contains less than 1% amide impurity and less than 1% desmethylcitalopram impurity after isolation from the reaction mixture.

2. A process as claimed in claim 1 wherein the phosphorous oxyhalide is phosphorous oxychloride.

3. A process as claimed in claim 1 wherein the phosphorous oxide is phosphorous pentoxide.

4. A process as claimed in claim 1 wherein in step (a), the ratio of the cyanide reversal agent to the crude 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base is in the range from 0.1 to 5.

5. The process as claimed in claim 4 wherein, the ratio is in the range between 0.1 to 2.

6. The process as claimed in claim 4 wherein, the ratio is in the range between 0.2 to 2.

7. A process as claimed in claim 1 wherein step (a) is carried out in an aprotic organic solvent.

8. A process as claimed in claim 7 wherein the aprotic organic solvent is polar or non-polar.

9. A process as claimed in claim 7 wherein the aprotic organic solvent is selected from group consisiting of ethers, halogenated solvents, aliphatic hydrocarbons, aromatic hydrocarbons, esters, nitirles and nitro compounds.

10. A process as claimed in claim 9 wherein the aromatic hydrocarbon solvent is selected from toluene and xylenes.

11. A process as claimed in claim 9 wherein the ether is selected from tetrahydrofuran and dioxane.

12. A process as claimed in claim 9 wherein the halogenated solvent is selected from a group consisting of dichloroethane, dichloromethane, chlorobenzene, and dichlorobenzene.

13. A process as claimed in claim 9 wherein the aliphatic hydrocarbon is selected from hexane and cyclohexane.

14. A process as claimed in claim 9 wherein the ester is selected from the group consisting of methyl acetate, ethyl acetate and benzyl acetate.

15. A process as claimed in claim 9 wherein the nitirle is selected from acetonitrile and benzonitrile.

16. A process as claimed in claim 9 wherein the nitro compound is selected from nitromethane and nitrobenzene.

17. A process as claimed in claim 1 wherein step (a) is carried out at ambient to 200^0C for 1 to 20 hours.

18. A process as claimed in claim 17 wherein step (a) is carried out at 50 to 150°C for 1 to 5 hours.

19. A process as claimed in claims 1 to 18 substantially as herein described and illustrated by examples 1 to 4.

Dated this 28th day of November, 2002.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED

ABSTRACT

The present invention provides a process for preparation of 1-[3-(dimethyl amino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, such that the unwanted amide impurity gets converted to the desired product viz. 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, along with simultaneous removal of desmethylcitalopram impurity.

To

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